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REVIEW

Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis

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Keywords

Clinical symptoms • COVID-19 • Meta-analysis

Summary

Introduction. *COVID-19 is an emerging infectious disease. The study about features of this infection could be very helpful in better knowledge about this infectious disease. The current systematic review and meta-analysis were aimed to estimate the prevalence of clinical symptoms of COVID-19 in a systematic review and meta-analysis.*

Methods. *A systematic review using Medline/PubMed, Scopus, and Google scholar has been conducted. In the current systematic review and meta-analysis, the articles published in the period January 1, 2020, to April 2, 2020, written in English and reporting clinical symptoms of COVID-19 was reviewed. To assess, the presence of heterogeneity, the Cochran's Q statistic, the I^2 index, and the tau-squared test were used. Because of significant heterogeneity between the studies the random-effects model with 95% CI was used to calculate the pooled estimation of each symptom prevalence.*

Results. *The most common symptoms in COVID-19 patients include: Fever 81.2% (95% CI: 77.9-84.4); Cough: 58.5% (95% CI: 54.2-62.8); Fatigue 38.5% (95% CI: 30.6-45.3); Dyspnea: 26.1% (95% CI: 20.4-31.8); and the Sputum: 25.8% (95% CI: 21.1-30.4). Based on the meta-regression results, the sample size used in different studies did not have a significant effect on the final estimate value ($P > 0.05$).*

Conclusions. *Considering the main symptoms of COVID-19 such as Fever, Cough, Fatigue, and Dyspnea can have a key role in early detection of this disease and prevent the transmission of the disease to other people.*

Introduction

The World Health Organization (WHO) described Coronavirus 2019 (COVID-19) as a public health emergency. The international concern of COVID-19 is more in comparison to Severe Acute Respiratory Syndrome (SARS), which previously was pandemic in 2003 [1]. Coronaviruses are important pathogens that can affect the lower respiratory tract in humans and can cause diseases ranging from a simple cold to severe infection with up to 50% lethality [2]. The COVID-19 is a highly contagious infectious disease and one infected person can infect an average of three other people [3] which is higher than that for SARS (1.7-1.9) and MERS (< 1), suggesting that SARS-CoV-2 has a greater potential for being outbreak. Evidence suggests that there are many similarities between COVID-19 and SARS. About 79.5% of the similarities in the genome sequence of these two viruses have been reported [4]. COVID-19 can spread in the community more easily than MERS and SARS because of the less severe clinical picture of it [5]. Although the disease is mild in most people, in some patients, especially those with other underlying diseases, there may be a respiratory failure, arrhythmias, shock, Kidney failure, cardiovascular damage, or liver failure [6, 7]. Currently, there is no effective antiviral treatment for the disease and only supportive care may be helpful [7] The case fatality rate (CFR) of COVID-19 was reported to be 3.8% but it can differ in patients who have comorbidities [8]. The CFR of COVID-19 is lower than that of SARS and that of MERS[5]. The most common symptoms are fever, cough, and myalgia or fatigue [9]. Although the clinical symptoms of the disease are nonspecific, understanding the symptoms is essential. Patient with fever and upper respiratory tract symptoms with lymphopenia or leukopenia should be considered as suspected [9] Patients may present with diarrhea a few days before the fever. A slight number of patients may report a headache [10]. Diarrhea is more common in SARS [5].

Combining the results of studies that have focused on the prevalence of COVID-19 related symptoms could be helpful in the best identification and diagnosis of infection. Because of the importance of symptoms in the identification of COVID-19 infection the current study was aimed to estimate the prevalence of Clinical Symptoms of COVID-19 in a systematic review and meta-analysis.

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Materials and methods

Eligibility criteria

All articles published in the period January 1, 2020, to April 2, 2020, written in English and reporting clinical symptoms of COVID-19 was reviewed. Review articles as well as articles that lacked original data or reported incomplete data were excluded.

Information sources and search strategy

We conducted a systematic review using Medline/PubMed, Scopus and Google scholar. The following search terms used: "Clinical features", "COVID-19", "coronavirus disease 2019", "coronavirus disease-19", "2019 novel coronavirus disease", "severe acute respiratory syndrome coronavirus", "clinical symptoms", "clinical characteristics" and "clinical manifestations". The searches were concluded by April 2, 2020, and two researchers independently assessed search results. References of related papers were also searched for other relevant articles to enhance the search strategy.

Study selection

After performing the search strategy some records were excluded because of Duplicates and unrelated. After that, the records screened based on abstracts and titles. The full text of related articles was then assessed according to the inclusion and exclusion criteria. Observational studies that reported clinical symptoms were included in the meta-analysis.

Data collection process and data items

Data including the type and date of publication, country, the sample size, age, and clinical symptoms of COVID-19 were extracted independently by two authors. A third person checked the article list and data extractions to ensure there were no duplicate articles and also resolved discrepancies about study inclusion.

Assessment of methodological quality

To assess the study quality of the case series studies the Institute of Health Economics (IHE) was used [11]. Also, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies was used assessment quality of the cross-sectional and cohort studies.

Meta-regression analysis

To assess the effect of sample size on pooled estimations the meta-regression analysis was used.

Statistical approach

To assessment, the presence of heterogeneity, the Cochran's Q statistic, the I^2 index, and the tau-squared test were used. Due to the difference in the age of patients, we perform subgroup analyzes in different age groups. Because of the presence, the significant heterogeneity between the studies the random-effects model with 95% CI was used to calculate the pooled estimation of symptoms prevalence. The data were analyzed using stata version 11.0.

Results

In the current systematic review and meta-analysis, 54 studies that estimated the symptoms related to COVID-19 were included in the final analysis (Tab. I). After searching PubMed and Google Scholar electronic databases, 1,498 possibly relevant articles were identified; 1,397 articles were removed due to unrelated to study purpose and duplication. Of the remaining 101 articles, 45 were excluded after screening based on abstract and title and 2 articles removed because of lack of needed information. Finally, 54 articles were included in the final meta-synthesis (Fig. 1).

Tab. I. Characteristics of the included studies on effective factors on mortality COVID-19, 2020.

Id	First author	Country	Design	Sample size
1	Dawei Wang [12]	China	Case series	138
2	Chaolin [13]	China	Cross-sectional	41
3	Chen [14]	China	Cross-sectional	99
4	Chung [15]	China	Cross-sectional	21
5	Chen [16]	China	Cross-sectional	29
6	Wang [12]	China	Cross-sectional	138
7	Kui [17]	China	Cross-sectional	137
8	Chang [18]	China	Cross-sectional	13
9	COVID-19 team Australia [19]	Australia	Cross-sectional	15
10	Li et al. [20]	China	Case series	24
11	Feng [21]	China	Case series	21
12	Zhang [22]	China	Case series	9
13	Feng [23]	China	Case series	15
14	Wang [24]	China	Cross-sectional	34
15	Xiaobo[25]	China	Cross-sectional	52
16	Jiong Wu et al. [26]	China	Cross-sectional	80
17	Zonghao Zhao [27]	China	Cross-sectional	77
18	Wen Zhao [28]	China	Cohort study	77
19	Wenjie Yang [29]	China	Cohort study	85
20	Matt Arentz [30]	USA	Case series	21
21	Ying Huang [31]	China	Retrospective	36
22	G Jian-ya Lei Liu [32]	China	Retrospective	51
23	Tao Chen [4]	China	Cohort	274
24	jin Zhang [33]	China	Cross-sectional	242
25	Shijiao Yan [34]	China	Retrospective	168
26	Jian Wu [35]	China	Retrospective	80
27	Yang Xu [36]	China	Retrospective	69
28	Fei Zhou [37]	China	Retrospective	191
29	Zenghui Cheng [38]	China	Retrospectively	11
30	Youbin Liu [39]	China	Retrospective	291
31	Yanli Liu [40]	China	Retrospective	109

continues

follows

Tab. I. Characteristics of the included studies on effective factors on mortality COVID-19, 2020.

32	Yonghao Xu [41]	China	Retrospective	45
33	Lang Wang [42]	China	Cohort	339
34	Zhichao Feng [43]	China	Cohort	141
35	Guo-Qing Qian [44]	China	Retrospective	91
36	BarnabyEdward Young [45]	Singapore	Case series	18
37	Ying Wen [46]	China	Retrospective	417
38	Jiaqiang Liao [47]	China	Retrospective	46
39	Xu Chen [48]	China	Cohort	291
40	Penghui Yang [49]	China	Cohort	55
41	Jie Liu [50]	China	Retrospective	64
42	Hang Fu [51]	China	Cross-sectional	52
43	Heshui Shi [52]	China	Cross-sectional	81
44	Wei Zhao [53]	China	Retrospective	101
45	Hua Fan [54]	China	Cohort	47
46	Ling Hu [55]	China	Retrospective	323
47	X. Zhao [56]	China	Cross-sectional	80
48	Zhaowei Chen [57]	China	Retrospective	89
49	Huijun Chen [58]	China	Retrospective	9
50	Rachael Pung [59]	Singapore	Retrospective	17
51	Wanbo Zhu [60]	China	Retrospective	116
52	Xiaoping Chen [61]	China	Retrospective	123
53	W. Guan [62]	China	Cross-sectional	1,099
54	Xi Xu[63]	China	Retrospective	90

According to the results of the analysis, the most common symptoms in patients with coronavirus include:

- Fever 81.2% (95% CI: 77.9-84.4);
- Cough: 58.5% (95% CI: 54.2-62.8);
- Fatigue: 38.5% (95% CI: 30.6-45.3);
- Dyspnea: 26.1% (95% CI: 20.4-31.8);
- and the presence of Sputum: 25.8% (95% CI: 21.1-30.4).

Other results are shown in Table II and Figure 2. Figure 2 presents the pooled estimation of some symptoms among COVID-19 patients.

Meta-regression analysis

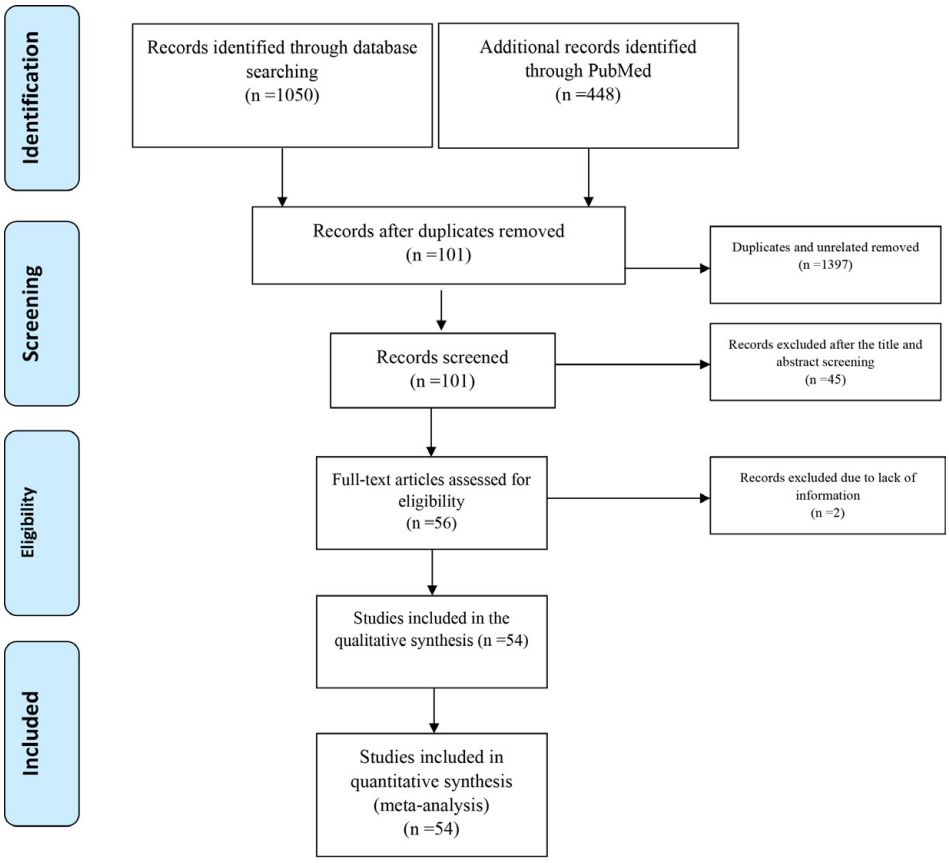
Based on the meta-regression results, the sample size used in different studies did not have a significant effect on the final estimate value ($P > 0.05$).

The distribution of the estimated prevalence of different symptoms according to sample sizes as shown in Figure 3.

The diagrams below show the percentage distribution of symptom estimation based on the volume of different samples.

Based on these charts, the estimated amount of chest pain, cough, dyspnea, hemoptysis, and fever with decreasing sample size showed a decreasing trend, while other symptoms showed an increasing trend with increasing sample size.

Fig. 1. PRISMA Flow Diagram for included studies in the current meta-analysis.



Tab. II. The prevalence of different symptoms among COVID-19 patients according to age groups.

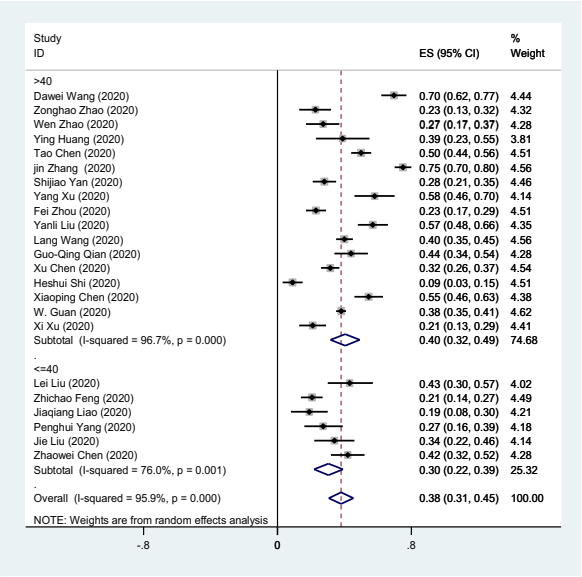
Symptom	Number of studies	Sample size	Pooled estimation			I^2 (%)	P	T^2
			< 40 years of old	> 40 years of old	Total			
Chest tightness	14	1,967	8.1 (3.7-12.6)	20.1 (9.6-30.6)	17 (13.1-25.4)	96.8	< 0.001	0.01
Cough	54	6,380	53.5 (44.3-62.7)	61.2 (56.3-66.1)	58.5 (54.2-62.8)	91.7	< 0.001	0.02
Diarrhea	36	4,995	3.5 (2.1-4.9)	8.6 (6.5-10.6)	7.6 (5.9-9.2)	83.9	< 0.001	0.001
Dyspnea	27	3,388	8.8 (2.6-15)	31.4 (24-38.7)	26.1 (20.4-31.8)	97.4	< 0.001	0.02
Fatigue	22	3,803	30.5 (21.9-39.1)	38.6 (29.9-47.2)	38.5 (30.6-45.3)	95.5	< 0.001	0.02
Fever	53	5,298	78.1 (73.3-82.8)	83 (79.1-86.9)	81.2 (77.9-84.4)	92.6	< 0.001	0.01
Hemoptysis	9	1,998	1.9 (0-4.6)	1.8 (0.008-2.9)	1.7 (0.008-2.6)	46.9	< 0.001	0.05
Headache	34	5,129	9.2 (5.4-13.1)	9.5 (7.1-12.0)	9.5 (7.5-11.6)	88.7	< 0.001	0.002
Myalgia	37	4,676	19 (14-23.9)	19.4 (14.9-24.0)	20.1 (16.5-23.7)	91.5	< 0.001	0.009
Shortness of breath	13	1,828	17.3 (3.6-30.1)	19.3 (11.2-27.5)	18.5 (12-24.9)	93.3	< 0.001	0.01
Sore throat	29	3,906	15 (9.6-20.4)	14.5 (10.9-18.2)	15 (12.1-18.0)	86	< 0.001	0.004
Sputum production	28	3,677	21 (15.4-26.7)	28 (22-34.1)	25.8 (21.1-30.4)	91	< 0.001	0.01

Discussion

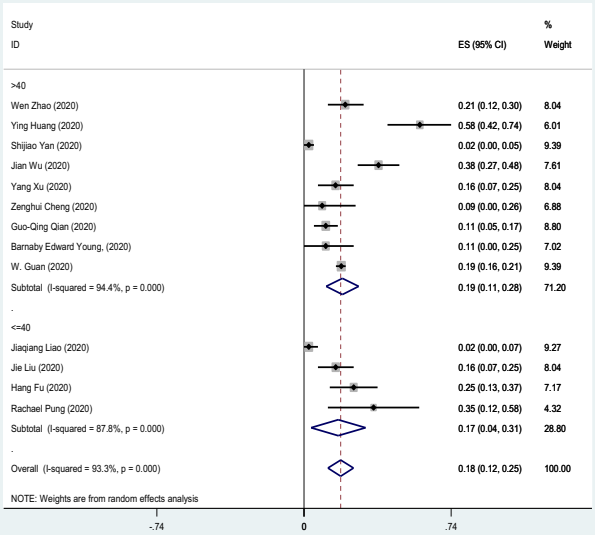
The COVID-19 is a new highly contagious infection that threatens people of all countries [64].

The clinical presentation of COVID-19 is wide, from asymptomatic infection to severe fatal diseases [14] Considering the shortage of diagnostic kits around the world this systematic review seems necessary, to find the clinical presentation of COVID-19 and using them in early diagnosis of this infection [13]. Unfortunately, there is no treatment for this virus, and patients' treatment is just focused on supportive care. On the other hand, the limited number of critical care centers and mechanical ventilation in the world culminates in high concern for the health care system [7]. To date, over 1,607,912 cases have been reported worldwide and from different countries [65]. To deal with such an emerging infectious disease, there an urgent need to identify and determine factors associated with the evolution of the disease and its outcomes. In this Systematic Review and Meta-Analysis study, we reported the clinical symptoms of COVID-19. Although the 2019-nCoV sequence is not the same as the other two viruses (SARS-CoV and MERS-CoV) that were pandemic in 2003 and 2012, respectively, they are somewhat similar in pathogenesis [66, 67]. Cytokines may play a role in human coronavirus infection. Indirect evidence suggests that in the second phase of 2019-nCoV infection: high fever, pneumonia, and hypoxemia occur despite a significant reduction in viral load [68]. In this systematic review and meta-analysis study, the clinical symptoms of COVID-19 were examined to provide a better understanding of the disease. The most common symptoms were fever and, cough, and fatigue that was consistent with the general symptoms of a viral infection and pneumonia. Similar to previous studies [25, 62], the present study showed that fever in 81.2% of cases, cough in 58.5% of cases, and fatigue in 38.5% of cases. Fever is the most common symptom in patients with COVID-19, but not all patients had fever [13, 69]. The fever is an alarming sign of the disease, vomiting, and fever (above 39 degrees) are usually associated with more severe illness and more length of stay in the hospital. Fever is less common in COVID-19 than in SARS and MERS [34, 70]. Therefore, more attention should be paid to COVID-19 patients who do not have fever as a source clue of infection, and if the surveillance system relies only on fever in patients, then some patients will be missed [71]. Diarrhea, myalgia, hemoptysis, and sore throats were less common symptoms in this review, these results were similar to those obtained for other viruses, such as SARS and MERS [26]. This may indicate that COVID-19 can also be classified as a similar infection to SARS and MERS infection, which targets the cells of the lower respiratory tract system. Although nasopharynx is theoretically the first organ infected with the COVID-19, a recent study [13] showed that infected individuals rarely show present upper respiratory symptoms at the onset of the infection. This suggests that the virus mostly targets the cells of the lower respiratory tract cells [72]. Research and clinical findings suggest that SARS-CoV-2 may be colonized in the nasopharynx but the immune system cannot identify COVID-19 in the early stages. Therefore, the virus can be removed from the body with its through natural reactions, including sneezing and runny nose. This demonstrates the importance of accurately

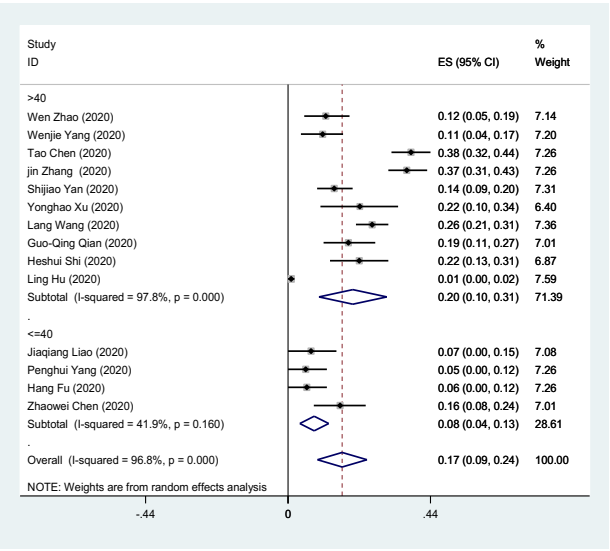
Fig. 2. The forest plots of some symptoms among COVID-19 patients.



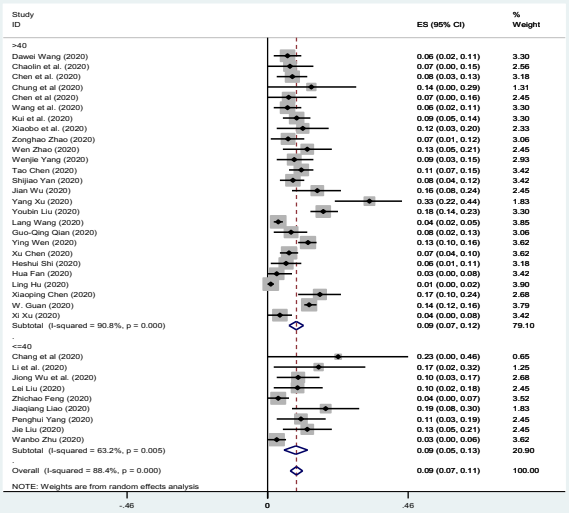
Fatigue



Shortness of breath



Chest tightness



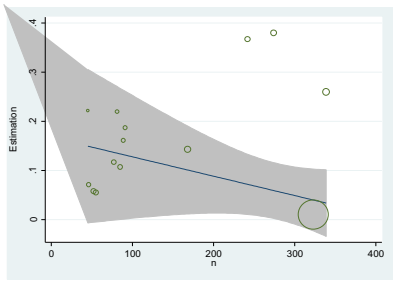
Headache

identifying COVID-19 symptoms at admission. Especially considering that studies have suggested the possibility of transmission of the disease by a healthy carrier [73]. This may be one of the reasons why COVID-19 is more contagious than SARS.

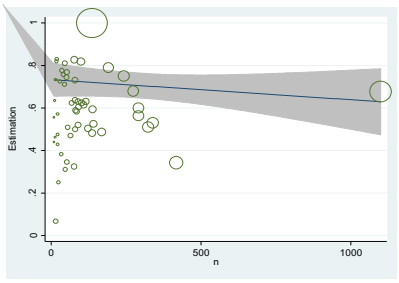
On the other hand, the lower incidence of early respiratory symptoms may be due to the presence of a pathogenic latency of SARS-CoV-2. Although gastrointestinal symptoms, especially diarrhea, were rare in the current study, the results of a study have shown that the SARS-CoV-2 virus can be isolated from the fecal samples of patients with gastrointestinal symptoms [74]. In another study, the SARS-CoV-2 virus has been isolated in a rectal swab of patients whose RT-PCR test results were negative with a throat swab sample [44]. Therefore, simultaneously sampling from throat and rectal may be useful, especially in patients with gastrointestinal symptoms. This review has some limitations which should be considered when interpreting the results. Most of the available studies for inclusion are from China. However the present study was done without any language restrictions and based on a comprehensive search strategy, only English electronic databases were searched; thus, it is likely that some related non-English papers have been missed.

Fig. 3. The distribution of estimated prevalence of symptoms according to different sample sizes (the X and Y axes are the sample size and estimated prevalence respectively).

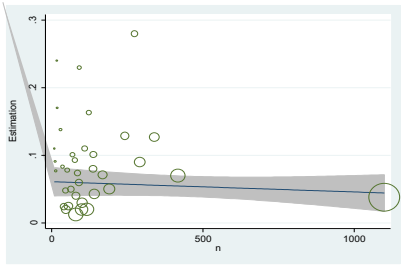
Chest tightness



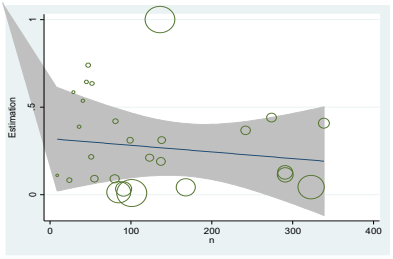
Cough



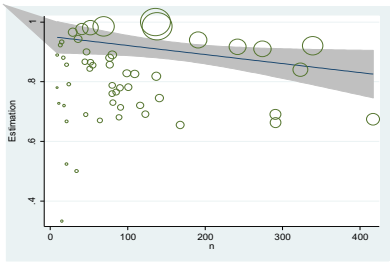
Diarrhea



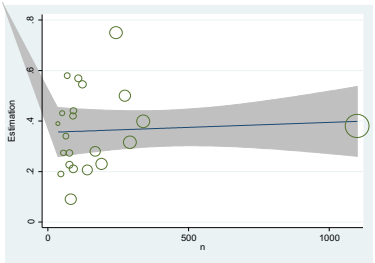
Dyspnea



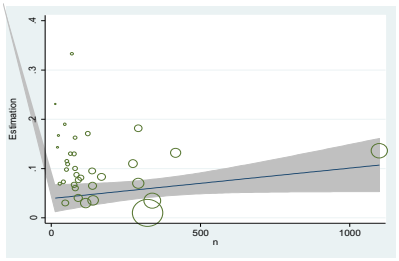
Fever



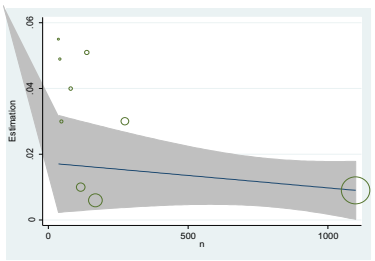
Fatigue



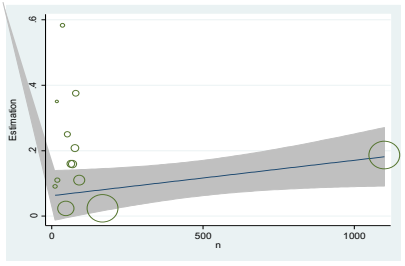
Headache



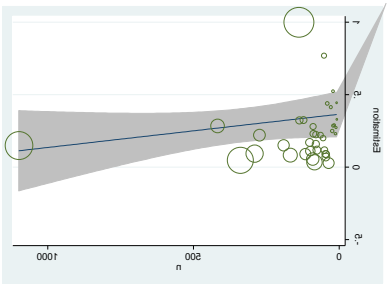
Hemoptysis



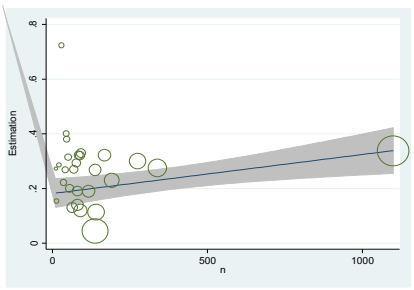
Shortness of breath



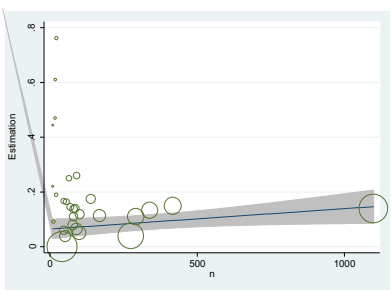
Myalgia



Sputum production



Sore throat



Conclusions

Due to the rapid spreading of this infection, the lack of diagnostic tools, and limited intensive care units in the world, the use of other factors such as the clinical features of COVID19 can serve to give early warning for the appropriate interventions and decrease the number of death of COVID-19. So considering the main symptoms of COVID-19 such as Fever, cough Fatigue and Dyspnea can have a key role in early detection of this disease.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

YA and MS formulated the research questions, designed the study, developed the preliminary search strategy, conducted the quality assessment, methodology, formal analysis, prepare drafts of the manuscript, review and editing, MT and HH refined the search strategy by conducting iterative database queries and incorporating new search terms, searched and collected the articles, re-viewed the manuscript content. Data extraction and prepare drafts of the manuscript. All authors critically reviewed the manuscript content. All authors have read and approved the final version of the manuscript.

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